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Is Afrin (Oxymetazoline) A Safe And Effective Drug In Normal, Healthy Adults With Reference To Nasal Congestion And The Nasal Response?

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Is Afrin (Oxymetazoline) A Safe And Effective Drug In Normal, Healthy Adults With Reference To Nasal Congestion And The Nasal Response?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not, "Is Afrin (Oxymetazoline) a safe and effective drug in normal, healthy adults with reference to nasal congestion and the nasal response?"

STUDY DESIGN: Review of three English language primary studies published in 1997, 1999, 2003.

DATA SOURCES: Randomized, controlled studies (double-blind, placebo-controlled) testing the efficacy and safeness of Afrin in comparison to a placebo group, were found using the PubMed database.

OUTCOMES MEASURED: Nasal patency, congestion, degree of nasal blockage, and symptoms (quantity, consistency, color of nasal secretions, turbinate size/color) were measured through patient diary card symptom scores, visual analogue scales, and clinical nasal visual examinations.

RESULTS: The Morris et al and Watanabe et al studies found that the subjective measurements and nasal examinations did not show clinically significant signs of rhinitis or differences between treatment groups after using Afrin. A clinically significant decongestant effect of Afrin was noted at each visit in all three RCT's. Bickford et al reports that symptoms of congestion decreased significantly after using Afrin but not after using the placebo. Morris et al and Watanabe et al found no signs of increased tolerance to Afrin, but evidence of rebound nasal congestion was reported after 3 days of Afrin treatment in the Morris study and no significant rebound nasal congestion was discovered by Watanabe et al after 4 weeks treatment.

CONCLUSIONS: All three RCT's showed that Afrin is effective in treating nasal congestion in normal, healthy adults. After subjects were treated with various doses of Afrin nasal spray, no clinically significant nasal congestion was found in any of the treatment groups. Morris et al and Watanabe et al found that there was no tolerance to the medication after using repeated doses. However, Morris et al found rebound nasal congestion after 3 days of use, whereas Watanabe et al found no rebound congestion after using various doses of Afrin for 4 weeks. Further research is needed to determine the appropriate length of treatment and possible side effects (rebound congestion) of Afrin.

KEY WORDS: Afrin; Oxymetazoline; Nasal Congestion; Adults

INTRODUCTION

Nasal congestion is an extremely common problem and complaint, affecting the majority of the population including each gender, race and age group across the world. Due to the numerous etiologies of nasal congestion and acute rhinitis, there are a myriad of treatment options to help ameliorate this problem. Therefore, treatment decisions can become quite difficult for both the consumer and provider. It is important to know which drugs not only provide the best treatment and relief, but those that have minimal side effects and maximum safety. This systematic review analyzes three placebo-controlled, double-blind, randomized controlled trials in normal, healthy men and women, age 16 and above, in order to determine the efficacy and safeness of Afrin (Oxymetazoline) with reference to nasal congestion and the nasal response.

The prevalence of nasal congestion is increasing worldwide, now including more than 10-40% of the total population.[1] In 2003, a Gallup poll found that >50% of Americans are suffering from nasal congestion and will self medicate to relieve their symptoms.[1] Allergic rhinitis has been identified as the most common cause of nasal congestion, affecting at least 40 million (>20%) of Americans today.[2] Around 1 in 7 adults (14%), >18 years of age, have been diagnosed with allergies, with more than 60% of those patients reporting daily nasal congestion.[1] "The apparent increase in the prevalence of allergic rhinitis in studies worldwide highlights the need for more effective treatment options for allergic rhinitis…congestion in particular."[1]

The economic impact of nasal congestion alone is currently unknown. Research focuses primarily on the causes, most frequently allergic rhinitis and rhinosinusitis, which have nasal congestion as their most common symptom.[1] In 2011, $5.3 billion/year was estimated as the total direct and indirect cost of allergic rhinitis alone.[2] However, there are several other co-

morbidities, such as asthma, that encompass nasal congestion as a symptom as well. The increasing prevalence also increases the number of healthcare visits per year. In 2005, there were more than 13 million office visits in which the patient presented with nasal congestion as a chief complaint.[1] In 2006, allergic rhinitis alone accounted for >12 million office visits per year.[1] These staggering numbers help to recognize the increased need for an effective and safe fix.

Currently, many treatment options are available; however, both patients and providers remain unsure as to which products are best. Current guidelines exist regarding the length of treatment for nasal congestion with reference to rebound complications, but the precise mechanism of rebound congestion, and other complications is still unknown.[2] Different drugs and the components within each treatment can lead to various side effects when used for different periods of time and further research must still be conducted to determine which drugs are most appropriate.[2]

The most commonly used treatments for nasal congestion include oral antihistamines, decongestants, or both as needed.[2] Depending on the source of the congestion, different medications within certain classes are used. For example, an intranasal steroid spray is frequently used in cases of chronic congestion.[2] Other treatment options include: 2nd generation antihistamines, intranasal antihistamine sprays, leukotriene receptor agonists, intranasal Cromolyn, intranasal anticholinergic sprays, short courses of corticosteroids, and first generation antihistamines.[2] Afrin falls within the nasal decongestant class. It works by narrowing the blood vessels within the nasal canal.[2]

The widespread usage of nasal decongestants like Afrin, has led to increasing concerns of abuse, rebound complications such as nasal congestion, tachyphylaxis, and nasal mucosa

swelling, tolerance, efficacy and safeness.[3] The amount of time remains unclear as to how long a nasal decongestant can be used for, and the correct dosage prior to developing undesirable effects.[3] Afrin is compared to placebos in various dosages over different periods of time in order to determine its safety and efficacy, with reference to nasal congestion and the nasal response.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not, "Is Afrin (Oxymetazoline) a safe and effective drug in normal, healthy adults with reference to nasal congestion and the nasal response?" Recent studies have shown that Afrin is effective in treating acute nasal congestion, but it remains unclear as to the correlation between prolonged use of the drug and rebound complications.

METHODS

Certain criteria were used to select similar studies in order to obtain more specific, accurate results. Each study selected focused on a population consisting of normal, healthy adult men and women 16 years of age or older. All three articles concentrated upon the intervention Afrin (Oxymetazoline), a topical decongestant nasal spray, and compared the effects of Afrin at varying dosages to the effects of a placebo. Morris et al[3] is a double-blind, placebo- controlled randomized controlled trial that studied 7 days of Afrin (0.05%) nasal spray treatment in subjects that received either daily Afrin (0.05%), intermittent Afrin (0.05%) morning doses on days 1, 3, and 7 with all other doses placebo, or daily placebo doses for comparison. Bickford et al[4] is a double-blind, placebo-controlled, randomized controlled trial and crossover study that focused on the administration of Afrin nasal spray 0.5 mg ml^{-1} (0.9 mg to each nostril) in comparison to a placebo nasal spray made of saline solution 0.9% to each nostril. Nasal patency measurements were made up to an hour prior to medication delivery and up to 120 minutes post delivery.[4] The

crossover was measured 7-21 days later.[4] Watanabe et al[5] is a double-blind, placebo-controlled randomized controlled trial that used 0.05% Afrin nasal spray, 2 sprays (0.1 ml/spray) to each nostril 3 times daily and compared it to a matched placebo nasal spray over a 4 week period. In this study, both the Afrin and the placebo nasal spray contained the chemical benzalkonium chloride 0.1%.[5] Each study measured nasal patency, nasal congestion, degree of nasal blockage, and symptoms including: quantity, consistency, color of nasal secretions, and turbinate size and color.[3,4,5]

In order to successfully locate articles pertaining to Afrin's efficacy and safeness with similar subject populations, a detailed and refined search was conducted using the key words, "Afrin," "Oxymetazoline," "Nasal congestion," and "Adults." Several databases were reviewed including OVID, Medline, Cochrane and PubMed; however, the articles analyzed in this paper were all located on the PubMed database. All selected articles are written in the English language and published in peer-reviewed journals. To narrow down the selection, each article was chosen based on relevance and patient-oriented evidence that matters (POEMS). Inclusion criteria for article selection included: randomized controlled trials published after 1996, POEMS, healthy adult patients $\geq$16 years of age, and minimal nasal airway resistance at baseline with normal nasal anatomy. Exclusion criteria includes: subjects with a past medical history of significant medical disease, seasonal allergies, nasal deformity/deviation, those who have taken recent medications such as antihistamines or decongestants, those who have had a recent URI or cold, and smokers. [3,4,5] The statistics reported are: p-values with a significant result <0.05, change in mean from baseline, mean +/- SD[3]; CI interval, ANOVA, CV[4]; and RRR, ARR, NNT[5].

Table 1: Demographics & characteristics of included studies for analysis of Afrin with reference to nasal congestion and the nasal response:

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Morris[3], 1997	RCT, double blind, placebo controlled	50	18-59	50 healthy subject volunteers between 18-59, male or female	NAR on day 1 >0.3 $Pa/cm^3/s$, hx of alcohol/ drug abuse; hx of any significant disease; rhinitis; deviated nasal septum, polyps, etc; not on current medications affecting nasal congestion; smoker; pregnant	N/A	7 days tx with Oxymetazoline (0/05% w/v) nasal spray; randomized to receive either daily(0.05%) or intermittent (0.05% with morning doses on days 1,3,7 and all other doses placebo)
Bickford[4], 1999	RCT, double blind, placebo controlled crossover study	20	18+ mean 27.3	20 healthy adult volunteers, male or female; minimal baseline NAR of at least 0.15 $Pa/s/cm^{-3}$	All subjects free of URI and no evidence of pharyngeal erythema, anatomic nasal obstruction/deformity; no sx of nasal congestion; could not have taken meds which may have influenced nasal congestion or interacted with Afrin	0	Nasal Spray Oxymetazoline 0.5 mg ml^{-1}(0.9 mg to each nostril) compared to nasal spray placebo (saline solution 0.9%) to each nostril
Watanabe[5], 2003	RCT, double blind, placebo controlled	30	16-60	Negative hx of seasonal/ perennial nasal sx other than common cold, non-smokers, normal lung function, normal nasal anatomy	Current smokers, taking concurrent medication, hx of use of topical or systemic nasal vasoconstrictors in last 6 months, hx of URI in last 4 wks, pmh of htn, CVD, or other significant medical problems	0	0.05% Oxymetazoline Nasal Spray: 2 sprays (0.1 ml/spray) to each nostril 3x daily over extended period of 4 weeks in comparison to placebo nasal spray

OUTCOMES MEASURED

Both the patient and clinician measured outcomes in order to determine symptoms of nasal congestion, blockage or patency. Morris et al[3] utilized subjective scaling of nasal patency through a visual analogue scale (VAS) and through a clinical examination by a physician. Bickford et al[4] also measured the outcomes through a 100-mm visual analogue scale with descriptors ranging from "nose completely clear," to "nose completely blocked," representing values of 0 and 100 mm respectively. Watanabe et al[5] had subjects complete a diary card of nasal symptoms and undergo a clinical examination. The card included: nasal blocking (scale 0-4), 0= no symptoms, 1=mild blockage, 2= moderate blockage, 3=severe blockage, 4= complete nasal blockage.[5]

RESULTS

The results pertaining to the primary outcome were presented as continuous data in all three studies. The continuous data presented in both the Morris et al[3] and Bickford et al[4] studies was unable to be changed into dichotomous form; however, the data presented in Watanabe et al[5] could be converted.

The Morris et al[3] RCT assessed the nasal response in 50 subjects after 7 days of Afrin regimes, by measuring nasal airway resistance (NAR) subjectively through a visual analogue scale (VAS) and clinical examination. The VAS and NAR subjective results were similar throughout the study with no separation between the treatment groups. Day 1 results (Table 2) illustrated a significant decongestant effect ($p < 0.05$) which occurred 30 minutes after drug administration and continued for up to 6 hours in both the daily and intermittent groups.

Table 2: Mean NAR change in baseline before and after treatment on Day 1:

	Mean NAR Pre Tx	**Mean NAR Post Tx**
Daily Afrin Tx Group	0.23 ± 0.05 Pa/cm^3 /s	0.15 ± 0.04 Pa/cm^3 /s
Intermittent Afrin Tx Group	0.22 ± 0.07 Pa/cm^3/s	0.15 ± 0.04 Pa/cm^3 /s
Placebo Group	0.26 ± 0.09 Pa/cm^3 /s	0.39 ± 0.35 Pa/cm^3 /s

However, the change in baseline of the mean NAR for the placebo group increased significantly ($p<0.05$). [3] The change from baseline was higher on Day 3 and 7 than on Day 1 for the daily and intermittent groups. Oxymetazoline remained effective at reducing the NAR throughout all 7 days, showing its significant decongestant effect without the development of a drug tolerance. [3]

Table 3: Mean Baseline NAR on Day 1 and Day 3 for Daily and Intermittent Treatment Groups:

	Daily: Baseline NAR	**Intermittent: Baseline NAR**
Day 1	0.23 ± 0.05 Pa/cm^3/s	0.22 ± 0.07 Pa/cm^3/s
Day 3	0.38 ± 0.23 Pa/cm^3/s	0.31 ± 0.15 Pa/cm^3/s

The significant change in mean baseline ($p<0.05$) in both the daily and intermittent groups indicates rebound congestion. The trend continued on to Day 7 but it was not statistically significant. The NAR baseline in placebo group also increased; however, it did not reach statistical significance as well. After treatment was completed, the intermittent group was the only group with significantly higher NAR on days 8 and 9 in comparison to day 1 ($p <0.05$). [3]

Bickford et al [4], a crossover trial, assessed symptoms of congestion through a visual analogue scale (CON, range 0-100) and the results were illustrated by the AUC showing a change from baseline value. When referring to the efficacy variables, the baseline values were similar on both days of the crossover studies. The nasal airway resistance (NAR) and subjective CON values indicating symptom scores, remained unchanged after the placebo, but fell significantly after the Oxymetazoline at all times 2 hours post dosing. Both the NAR AUC and

the CON AUC showed significant differences between the Oxymetazoline and placebo groups, $P< 0.001$ and $P= 0.012$ respectively.[4]

Watanabe et al[5] is a randomized double-blind, placebo-controlled continuous study in which its data is capable of being converted into dichotomous format (see Table 4). The treatment effects were analyzed using the Wilcoxon rank test. At baseline, nasal patency between the treatment groups was not statistically different and groups were matched for gender, baseline lung function and atopic status. After subjective diary symptom scores and clinical exams were completed post Oxymetazoline challenge, the results did not show a significant increase in subjective nasal blockage after 4 weeks of usage and 6 weeks of total monitoring for the Oxymetazoline or placebo groups. There was also a highly significant decongestant effect after each Oxymetazoline treatment. However, the subject diary symptom scores were unable to be analyzed numerically because the majority of the results showed a 0, indicating "no blockage" for both treatment groups at all points throughout the study. A possible trend in the placebo group was developing, showing mild and occasionally moderate nasal blockage but it was not significantly different between the groups. The clinical examination did not find significant changes in the nasal mucosa appearance, significant bleeding, or findings associated with rhinitis medicamentosa in either group.[5] Table 4 uses the evening measurements at the end of the 4 week treatment period, to analyze the outcome of nasal congestion for prevention.

Table 4: Analysis of RRR and NNT for Prevention in the Watanabe et al[5] study:

Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)
67%	93%	38.8%	26%	4

The NNT illustrates that for every 4 patients that are treated, 1 patient will be symptom free, therefore preventing a negative outcome such as worsening of symptoms or complications, when

compared to a placebo at 4 weeks. However, negative outcomes were not significant in this study.

Due to the limited adverse effects of Afrin and the lack of complications within all 3 studies, each study had a 100% compliance rate. On clinical exam, changes in the nasal mucosa were not found in any of the studies, and trends of rebound congestion were noted to be the only adverse effect found when using Afrin in healthy, normal adults.[3,4,5]

DISCUSSION

Afrin is one of the most commonly used medications to treat nasal congestion; however, the general population associates prolonged use of this medication with rebound effects and complications. According to Morris et al[3], prior studies have focussed on weeks, months or years of decongestant use and little research has been published on Afrin use for shorter periods of time. In 1985, the FDA recommended that decongestant products such as Afrin should be used for a maximum of 3 days and stated that these medications produce rebound congestion within hours of use.[3] However, their recommendation centered upon long term Afrin use in studies conducted more than 30 years ago. Current literature focussing upon short term decongestant use and its possible rebound effects remains unclear.

According to PubMedHealth[6], recent guidelines suggest using Afrin nasal spray every 10-12 hours as needed but no more than twice in a 24 hour period. Users are instructed to use the spray for no more than 3 days consecutively and a warning is given that if the drug is used for longer than the recommended period of time, the congestion can worsen, improve, or come back. Possible side effects include: burning, stinging, increased nasal discharge, dryness inside the nose, sneezing, nervousness, nausea, dizziness, headache, difficulty falling asleep or staying asleep, fast heartbeat or slow heartbeat.[6]

When referring to efficacy, Morris et al[3] showed that Afrin was just as effective in reducing the NAR on day 1 as on day 7 and Watanabe et al[5] found no significant increases in subjective nasal blockage after 4 weeks of treatment and for 2 weeks after discontinuation of the drug. All three studies found a highly significant decongestant effect, therefore indicating that not only is Afrin effective in eliminating nasal congestion, but Afrin does not cause a drug tolerance to develop after continual doses.

The safety of this drug remains unclear because some evidence, as seen in Morris et al[3], shows that Afrin may cause rebound congestion after 3 days of treatment, but Watanabe et al[5] found no evidence of rebound congestion or other side effects after 4 weeks of continuous dosing. In the Morris et al[3] study, the baseline NAR on day 3 was significantly greater than day 1 in both the daily and intermittent groups, but the baseline NAR differences between the treatment and placebo groups did not reach significance on any of the days. However, the rebound congestion on day 3 cannot be attributed to Afrin use alone because the baseline NAR increased over the course of the study in both the treatment and placebo groups. It is possible that the benzalkonium chloride in the placebo contributed to the rebound congestion by acting as a nasal irritant and reducing mucociliary clearance.[3]

While Morris et al[3] and Watanabe et al[5] recruited volunteers without a baseline nasal airway resistance, the Bickford et al[4] study used participants with a minimal NAR baseline, but still within the normal range, to increase the ability of detecting a significant decrease in NAR. In the Bickford et al[4] study, Afrin showed a significant decongestant effect in the subjective results that was further verified by parallel results of the objective measurements.[4]

Possible limitations to help explain variability within results include small sample sizes, the use of irritants and various substances in some of the placebo sprays, and subjective scaling.

It is possible that spraying a placebo into the nasal canal can lead to rebound congestion and further studies are needed to determine if the substances in the vehicle spray are responsible for causing rebound side effects. Subjective scaling is also not the most accurate way to detect congestion because perceptions of symptom severity can differ from person to person and symptoms can be affected by sensory changes as well as changes in NAR.

CONCLUSION

All three randomized controlled trials demonstrated that Afrin is an effective treatment in normal healthy adults with reference to nasal congestion and the nasal response. After subjects were treated with various doses of Afrin over different periods of time, no evidence of significant nasal congestion was found after continually using the drug, also showing that a tolerance to the drug does not develop. However, there was conflicting evidence regarding drug safety and appropriate length of treatment prior to developing side effects. Morris et al[3] found rebound congestion after 3 days of Afrin use, whereas Watanabe et al[5] found no evidence of rebound congestion after 4 weeks of use.

Future studies are warranted to determine the appropriate length of treatment, when side effects occur, and if they even occur at all. Current studies often use placebos that contain substances like benzalkonium chloride, which can lead to nasal congestion, possibly impacting the validity of the results. Research is indicated to determine if these substances, which can be found in both the placebo and Afrin nasal sprays, are causing rebound congestion. It is essential that appropriate length of treatment and adverse side effects be fully understood to help those who are suffering from nasal congestion feel that their symptoms are being treated adequately.

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